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PATREA L PABST
ARNALL GOLDEN & GREGORY
2800 ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET
ATLANTA GA 30309

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
08/970,045	Koren et al.	
Examiner	Group Art Unit	
Duffy	1645	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on Request for reconsideration and Amendment of 11-29-00.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-13 and 39-47 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 1-13 and 39-44 is/are rejected.

☒ Claim(s) 46 is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statem nt(s), PTO-1449, Paper No(s)._____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

2. The amendment filed 11-29-00 has been entered into the record. Claims 1-13 and 39-47 are pending and under examination.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

4. Any rejections or objections not maintained herein are withdrawn based upon Applicant's amendments.

Rejections Maintained

5. The rejection of claim 39 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in Paper No. 12, mailed 6-27-00 and reiterated below.

Claim 39 is drawn to the use of antibodies which bind HDL or LDL but do not cross react with LDL or HDL respectively. These antibodies do not apparently have written description support in the specification as originally filed. Applicants point to Example 8, page 63 of the specification for support of the above recited limitation. This is not persuasive. Example 8 does

not address "cross-reactivity" of antibodies nor convey the now claimed concept such that one skilled in the art would understand that applicants were in possession of the claimed invention at the time of filing.

6. Claims 1-12, 40, 41, 43, 45 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for resasons made of record in Paper No. 12, mailed 6-27-00.

As to claim 1 and every claim dependent thereon (2-11), the claims are still confusing since it is unclear that each of the first and second antibodies *must bind different lipoproteins or apolipoproteins in order to affect a ratio.* In the absence of such a recitation, the claims lack key elements which are required for an assay to result in the determination of a ratio of different lipoproteins or apolipoproteins. The insertion of "wherein the first and second monoclonal antibodies bind to either LDL, HLD or VLDL or to different apolipoproteins.." is insufficient to obviate the rejection because the first and second monoclonal antibodies bind LDL, HLD or VLDL. This recitation appears to require that the first and second monoclonal antibodies to bind a single lipoprotein. Thus is is unclear how a ratio of LDL to HDL is effected if both the first and second monoclonal antibodies bind the same lipoprotein. Amendment of the claim to recitie language such as --wherein the first and the second monoclonal antibody each bind different lipoprotiens seleced from the group consisting of LDL and HDL or wherein the first and the second monoclonal antibody each bind different apolipoproteins -- would provide for the concept that the first and second antibodies must each bind different lipoproteins or each bind different apolipoproteins.

As to claim 40, the claim still states "... separating the complexed antibody-lipoprotein particles from the biological sample.." which renders the claim unclear since it is unclear which complexes are separated and how. Applicants have appropriately amended step (a) to obviate the rejection with respect to Apo C-III and pan B antibody. However, the same concern is still apparent for the recitation of "... contacting the anti-Apo A-I antibody with the biological sample" in the latter half of the assay for HDL, applicants amendments have not resolved this issue in the latter half of the claim (see in particular step b, line 11).

As to claim 41, the claim still does not make it clear how the provided antibodies make it into the same sample, nor do they clearly delineate that population which is being separated for the later recitation in the second half of the assay for determining the amount of HDL. Applicants' amendments are insufficient to obviate the second half of this rejection. The determination of Apo E associated with HDL makes no sense because it references ApoB containing particles of step (c) and does not reference the provided Apo AI antibody step (c). What is the function of the provided Apo AI antibody present in the assay ? Apo B is not known to be associated with HDL lipoproteins as a result is is unclear how the combination of pan-Apo B antibody and anti-Apo E antibody acheives the determination of Apo E present in HDL particles.

As to claims 43 and 45, the claims are still indefinite. The rejection is maintained for reasons made of record. The elmination of the preamble does not provide for antecedent basis for the remainder of the claim still in question as set forth previously ".....". More explicitly, claim 43 recites "stable, conformation independent epitope..... specific lipoprotein", is language that has no basis in claim 42. As to claim 45, again language such as "recombinant antibodies, and monoclonal antibody fragments" still lack antecedent basis in claim 44.

7. The rejection of claim 46 under 35 U.S.C. 102(b) as being clearly anticipated by Curtiss et al (U.S. Patent 4,677,057, issued June 30, 1987) is maintained for reasons made of record in Paper No. 12, mailed 6-27-00.

Applicants' arguements have been carefully considered but are not persuasive. Applicants point to the characterization of the Apo AI and Apo AII antibodies on column 13 and column 14 of the Curtiss et al reference as not lipid independent. However, the examiner specifically cited the Apo AII antibody. Curtiss et al specifically teach that the Apo AII antibody bound all the Apo AII present in HDL (see column 13, lines 32-34 and see again column 22, lines 34-67) this meets the lipid independent or lipid associated with a specific lipoproten (i.e. HDL). Applicants err in asserting otherwize. The heterogenity of the Apo AI antibodies with respect to binding all HDL particles is irrelevent because the disclosed binding characteristics relied upon were for the Apo AII monoclonal antibody. The rejection is maintained. It is also noted that the recited features of the epitope are recited in the alternative (i.e. "or") and thus the claim structure does not require all the binding characteristics.

8. The rejection of claims 42-45 under 35 U.S.C. 103(a) as being unpatentable over Koren et al (Atherosclerosis, 95:157-170, 1992) is maintained for reasons made of record in Paper No. 12, mailed 6-27-00.

Applicants' arguements have been carefully considered but are not persuasive. Applicants' argue that neither Curtiss or Koren et al teach conformation or lipid independent antibodies. This is not persuasive with respect to Curtiss et al discussed above. As to Koren, the pan antibodies described by Koren et al also teach that the Apo B antibody, Apo AII antibody and the Apo CIII antibody allow for complete removal of all Apo AII containing and Apo C III containing density classes from normal and hyperlipidimic serum. Thus, these specific

antibodies also meet the criteria of binding as conformational epitope uninfluenced by lipid content of lipoprotein because the antibody binds the apolipoprotein regardless of the density class of the lipoprotein. As a result, Applicants' arguements are not persuasive.

New Rejections Based on Amendments to the Claims

9. Claims 1-13 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants have amended the claims to recite that the monoclonal antibodies bind the claimed apolipoprotien or lipoprotein in a "conformation and lipid content independent manner". While the specification supports the monoclonal antibody that binds to a stable, conformation independent epitope that is uninfluenced by the lipid content of the lipoprotein, apolipoprotien or lipid associated with a specific lipoprotein it does not provide for binding by an antibody in generic conformation and lipid content independent manner. The broader genus now claimed does not include the limimtation of "the epitope" must be "a stable, conformation independent epitope that is uninfluenced by the lipid content of the lipoprotein, apolipoprotien or lipid associated with a specific lipoprotein". The genus now recited was not conceived at the time of filing.

10. Claims 1-12, 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 1 and every claim dependent thereon (2-11), the claims recite a method of determining a relative ration of LDL to HDL and include as one of the first or second antibodies

antibodies that bind VLDL. It is unclear how the measurement of VLDL contributes to the relative ratios of LDL to HDL as reqired by the preamble.

As to claims 4-5, the claim recites "the antibodies comprise" but the independent claim recites at least two antibodies. Does applicant intend this to cover both antibodies or one antibody ? If both the antibodies comprise the recited deposited antibody, then it is not clear how the assay works because it can not determine a ratio.

As to claim 9, this claim is still confusing. It is unclear how this assay works to detect an apolipoprotein when a third antibody is coupled to a protein stain binds with an undefined apolipoprotein. Morover, their is a disaggreement with tenses, an antibody (singular) is provided but is reactive with the apolipoproteins (plural). The binding specificity of the antibody that is provided is unclear because it is unclear if the coupled antibody binds to one or both apolipoproteins, or to one or both lipoproteins ?

As to claim 12 and every claim dependent thereon, the claim remains indefinite because it is unclear as to which first of second antibody binds which apolipoprotein, the claim indicates that the third antibody binds one of the first and second monoclonal antibodies. Thus, the claim as written, can determine the apoliprotein bound by the first and third antibody or the apolipoprotiein bound by the second and the third antibody but it can not determine a relative concentration of at least two different aplioproteins as required by the preamble. As such the method still lacks steps to achieve the goal of the preamble. How is the second apolipoprotein measured and how is the ratio achieved. The lack of clear antecedent basis in these claims still renders it unclear as to what antibody binds what apolipoprotein and how the ratio is affected with respect to the two apolipoproteins. Additionally, it is unclear how the apolipoproteins are distinguished each from the other because the mixed sample contains at least two

apolipoproteins which have two antibodies bound and a third antibody immobilized. How is separate quantitation achieved. How are two separate apolipoproteins detected ? The method steps are missing unknown undefined critical elements which is required to achieve quantitation of two separate apolipoproteins.

As to claim 40, the claim lacks a step of detemining the amound of the amount of Apo C-III present in the VLDL in the Pan B-anti-ApoC-III complexed material in the sample, as such the method is incomplete as written because a ratio of two points can not be derived from a point that has not been determined.

11. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) in view of Koren et al (Atherosclerosis, 95:157-170, 1992).

The claims are drawn to measurement of a ratio of at least two apolipoproteins or the by immersing into the sample a solid phase material having separately immobilized thereon at least first and second monoclonal antibody molecules immunoreactive with at least two different apolipoproteins in a conformation and lipid content independent manner, removing the solid phase material, determining the amount of at least two different apolipoproteins in order to compare the amount that is specific for at least two different lipoproteins.

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992) teach a solid phase card based assay system which provides for analyzing a particular sample for different analytes (see column 2, lines 58-68; column 4, lines 50-55). The card provides a plurality of tabs. Each of the tabs has at least one receptor for the same analyte and may have a plurality of receptors for

different analytes. The receptors are immobilized (see column 6, lines 55-62) on the tab(s) thereby allowing the simultaneous assay of a plurality of analytes in a single sample. The receptors are selectively attached a prearranged locations to the support, and where the analyte is an antigen the receptor would be a specific antibody (see column 7, lines 54-62). The card-like support can be dipped into the sample (see column 8, lines 24-34). A sufficient time is allowed for the interaction of the analyte and the receptor, the support is washed. The washed support is developed by a variety of means using a probe containing solution to quantitatively or qualitatively establish the presence of the analytes. The detection is provided by a variety of means including sandwich immunoassay , development of a color reaction, radioactive assay etc (see column 6, lines 1-15). Fish et al teach how to make the binding reaction quantitative (see column 12, first and second full paragraphs). Fish et al teach that the card may be developed in the office under field conditions, or in the laboratory (see column 9, lines 15-16). Fish et al differ by not using a dipstick and using antibodies that bind in a conformation and lipid content independent manner.

Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988) teaches methods for the determination of Apolipoprotein B-100 (Apo B-100) to apolipoprotein AI (Apo AI) using enzyme linked immunoassay sandwich techniques wherein the monoclonal antibodies specific for Apo B-100 (page 30, lines 30-41) and Apo AI (page 27-28) are immobilized on a solid phase, contacted with a sample, and the bound lipoproteins or apolipoprotein were detected. The detection was performed with an enzyme-linked monoclonal or polyclonal antibodies specific for Apo B-100 and Apo AI. Scripps Clinic and Research Foundation also teach that the immobilized antibody, sample and detection antibody simultaneously (see pages 33-34, claim 6).

Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) teach the development of a simple dipstick measurement of apolipoproteins. Forster et al teach a sandwich assay for Apo AI or Apo B, wherein one of the antibodies is bound to the dipstick. The dipstick is immersed into the sample. After a certain amount of time the stick is removed and immersed in a developing reagent to detect Apo AI or Apo B. The presence of Apo AI or Apo B is detected using an enzyme-labeled second antibody or added to the sample a small amount of the corresponding enzyme-labeled apolipoprotein which acts as a tracer. Forster et al teach that Apo AI and Apo B are the major protein components of high-density lipoproteins (HDL) and low-density lipoproteins (LDL) respectively (i.e. the instant apolipoprotein). Forster et al teach that the dipstick test is being developed to test for an ApoB/AI ratio which has the advantage of use in on the spot testing in general practitioners' surgeries or out-patient clinics.

Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) teach that the ratios of ApoA-I/ApoB are helpful in the diagnosis and differential diagnosis of coronary heart disease.

Koren et al (Atherosclerosis, 95:157-170, 1992) teach pan monoclonal antibodies for ApoB, Apo AII, and Apo CIII apolipoproteins (see pages 162-163) and their use in immunoassays. Koren et al also teach Apo E antibodies, one that binds to HDL and LDL and the other that binds VLDL. The "pan antibodies" described by Koren et al, the pan Apo B antibody, Apo AII antibody and the Apo C III antibody allow for complete removal of all Apo AII containing and Apo C III containing density classes from normal and hyperlipidimic serum. Thus, these specific antibodies also meet the criteria of binding as conformational epitope uninfluenced by conformation lipid content of lipoprotein because the antibody binds the apolipoprotein regardless of the density class of the lipoprotein and it binds and removes all of the Apo B, Apo AII or Apo CIII present.

As to claims 1, 10 and 11, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the multi-analyte card sandwich immunoassay of Fish et al by separately immobilizing the monoclonal antibodies specific for Apo B-100 (page 30, lines 30-41) and Apo AI (page 27-28) and each of the pan B, AII and CIII monoclonal antibodies of Koren et al, at prearranged places on the solid support tab in order to simultaneously perform the sandwich immunoassays for any of the lipoprotiens of interest such as those of the Scripps Clinic and Research Foundation and Koren et al, by employing the modified card tab assay to quantitate and determine lipoprotein or apolipoprotein ratios because Forster et al teach that apolipoproteins can be measured by a simple dipstick immunoassay and provide the advantage of use in on the spot testing in general practitioners' surgeries or out-patient clinics, that Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) teach that the ratios of ApoA-I/ApoB are helpful in the diagnosis and differential diagnosis of coronary heart disease, multi-analyte testing would save substantial time and reagents, and the substitution of one solid phase for another is quite routine in the art. It would also have been *prima facie* obvious to one having ordinary skill in the art to substitute or add to the multianalyte card immunoassay, the monoclonal antibodies of Koren et al to assay for the apolipoprotein E or C III in combination with the Apo AI and Apo B100 in the multi-analyte method as combined *supra* because Koren et al teach monoclonal antibodies which bind ApoE and Apo CIII could be used in a solid phase immunoassay and the substitution of one analyte for another is routine in the art. One would have been motivated to substitute the other apolipoproteins in the method as combined in order to study their role, if any, in coronary artery disease or atherosclerosis. It is noted that the method as combined above uses three antibodies that bind specific apolipoproteins are conformation and lipid-content independent, the "pan antibodies". As to the

claims, it would have also been *prima facie* obvious to one of ordinary skill in the art to use antigen binding fragments or recombinant antibodies of the monoclonal antibodies in the method as combined above because these antibodies would function equivalently in the assay as combined and such substitutions are routine in the art.

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Koren et al (Atherosclerosis, 95:157-170, 1992) as applied to claims 1, 10 and 11 above, and further in view of Luca (EP 0 407 035, published 2/3/88.

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Koren et al (Atherosclerosis, 95:157-170, 1992) are set forth *supra*. The combination differs by not assaying for the presence of lipid associated with lipoproteins or apolipoproteins using as the detection means a lipid stain.

Luca teaches a method for the determination of lipid and/or apoprotein moiety of intact lipoproteins. Luca teaches capturing lipoproteins in a biological sample with an antibody (i.e. polyclonal, monoclonal claims 1-2; page 19) immobilized on a solid support which binds and epitope on an apolipoprotein and staining at least one fraction of the lipid contained in the lipid moiety of the captured lipoprotein by means of a lipid probe which becomes incorporated into the lipid moiety of the captured lipoprotein, detecting the measured signal form the incorporated or attached lipid probe and relating the signal identity to the amount of the fractions of the lipid

moiety. Luca teach that the determination of lipoproteins and lipids are important in the examination of coronary heart disease.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the multi-analyte solid phase card assay as combined *supra* by replacing the detection antibody with the lipid probe of Luca et al because Luca teach that lipid probes as a means for the determination and quantitation of lipid associated with an apolipoprotein in an intact lipoprotein as a means to study coronary heart disease and Fish et al teach that probes which provide for a color change are sufficient for analyte detection.

13. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990), Koren et al (Atherosclerosis, 95:157-170, 1992) and Luca (EP 0 407 035, published 2/3/88) and as applied to claim 6 above, and further in view of Mills et al (Laboratory Techniques in biochemistry and molecular biology, Volume 14, A Guidebook to Lipoprotein Technique; 1984, pages 472-478).

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990), Koren et al (Atherosclerosis, 95:157-170, 1992) and Luca (EP 0 407 035, published 2/3/88) are set forth *supra*. The combination differs by not assaying for the presence of lipid associated with lipoproteins or apolipoproteins using as the detection means a the lipid stains the lipid stains Oil Red O and Sudan Black B.

Mills et al teach conventional and routine methods of staining lipids using routine and conventional stains such as Oil Red O and Sudan Black B (page 473-475). Mills et al also teach that Sudan Black can be used to pre-stain lipoproteins in plasma.

As to claim 7, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute Oil Red O or Sudan Black B for the lipid stain in the method as *supra* for claim 10 because Mills et al teach that lipids are conventionally detected using the Oil Red O and Sudan Black B. As to claim 8, it would have been *prima facie* obvious to one of ordinary skill in the at the time the invention was made to pre-stain the sample lipoproteins in the method as opposed to subsequent staining of the lipoproteins using the prestaining method with Sudan Black B as taught by Mills et al because Mills et al teach that the lipoproteins in a plasma sample can be detected even if they are prestained.

14. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Koren et al (Atherosclerosis, 95:157-170, 1992) as applied to claims 1, 10, and 11 above, and further in view of Scripps Clinic (EP 0 257 778, published 2/3/88).

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) Koren et al (Atherosclerosis, 95:157-170, 1992) are set forth *supra*. The combination differs by not combining the labeled detection antibody with the sample prior to immersing the multi-analyte card into the sample.

Scripps Clinic (EP 0 257 778, published 2/3/88) teaches an indirect solid phase immunoassay for Apo B100 using two monoclonal antibodies wherein one monoclonal antibody is immobilized on a solid phase and the other labeled monoclonal antibody to a second epitope is added to the sample to form an immunoreaction mixture before contacting with the solid phase (page 13, see lines 38-42).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to mix the labeled detection/probe antibodies for any of the apolipoprotiens in the method as combined supra with the sample prior to the immersion of the multi-analyte solid phase card in the immunoassay as combined *supra* because Scripps Clinic teaches that (EP 0 257 778, published 2/3/88) the detection monoclonal antibody drawn to a second epitope on the apolipoprotein can be mixed with the sample prior to contacting with the solid phase and one would have been motivated to admix the detection antibody with the sample prior to immersing the solid phase multi-analyte card as combined to reduce the number of incubation steps and provide the advantage of reduction of assay time. One would have reasonably expected the modification to be successful because Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988) teach that the all the assay reagents could be present simultaneously.

15. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990)and Koren et al (Atherosclerosis, 95:157-170, 1992) as applied to claims 1, 10 and 11

above, and further in view of Curtiss et al (U.S. Patent 4,677,057, published June 30, 1987) is maintained for reasons made of record.

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Koren et al (Atherosclerosis, 95:157-170, 1992) are set forth supra. The combination differs by not assaying for other apolipoproteins (Apo AII), lipoproteins containing the apolipoproteins and determining the ratio of these.

Curtiss et al (U.S. Patent 4,677,057, published June 30, 1987) teach a solid phase immunoassays for Apo I and Apo AII using a monoclonal antibodies bound to a solid phase (see column 16, lines 36-68). Curtiss et al teach that the determination of Apo AI and Apo AII are potentially useful to determine the prognosis of atherosclerosis or coronary artery disease (see column 5, lines 36-40).

It would have been *prima facie* obvious to one having ordinary skill in the art to add all apolipoprotiens to the the solid phase dipstick immunoassay the multi-analyte method as combined *supra* because Curtis et al teach Apo AII was also an apolipoprotein marker for HDL and that the levels of Apo AI and Apo AII were potentially useful in the prognosis of atherosclerosis or coronary artery disease.

Response to Amendment

16. Applicants' arguements are largely moot in veiw of the new grounds of rejection set forth supra in view of Applicants' amendments. As to the Curtiss et al and Koren et al reference, the examiner points out that these references teach "pan" antibodies that bind all apolipoproteins

present irrespective of the density class of the lipoprotein containing the apoliporotein. Therefore the "pan" antibodies are conformation and lipid content independent. Applicants arguements that they are not specific for a specific lipoprotein is not persuasive for a ratio of two apolipoproteins as claimed.

Status of Claims

17. Claims 1-13 and 39-46 are rejected. Claim 47 is objected to as depending from a rejected base claim.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

19. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice

published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
March 7, 2001

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600